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Douglas J. Weber

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14. ABSTRACT
During the 12-month funding period, we completed a total of 7 acute experiments, with the goal of developing a technique for using multichannel microstimulation to activate several distinct groups of primary afferent neurons in the dorsal root ganglia (aim 1). The utility of multichannel microstimulation is for the encoding of information in the spatiotemporal patter of stimulation applied to the afferents (aim 2). To the effectiveness of afferent microstimulation, we recorded evoked neural activity in the somatosensory cortex during microstimulation with patterns that varied in 1) amplitude (stimulus current), 2) location (various channels within the DRG electrode array) and 3) rate (the frequency of microstimulation pulses applied to each DRG

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Report Title

Final report: A new animal model for developing a somatosensory neural interface for prosthetic limbs.

ABSTRACT

During the 12-month funding period, we completed a total of 7 acute experiments, with the goal of developing a technique for using multichannel microstimulation to activate several distinct groups of primary afferent neurons in the dorsal root ganglia (aim 1). The utility of multichannel microstimulation is for the encoding of information in the spatiotemporal patter of stimulation applied to the afferents (aim 2). To the effectiveness of afferent microstimulation, we recorded evoked neural activity in the somatosensory cortex during microstimulation with patterns that varied in 1) amplitude (stimulus current), 2) location (various channels within the DRG electrode array) and 3) rate (the frequency of microstimulation pulses applied to each DRG electrode). A summary of the most important results appears below. Key points are highlighted in bold italics font.

Key findings:

1) Nerve-cuff recordings of afferent responses to microstimulation revealed the range of microstimulation intensities that are needed to activate the mechanoreceptive neurons, such as muscle spindles, golgi tendon organs, and cutaneous afferents that mediate haptic and proprioceptive sensations.

2) We have recorded neural activity in the somatosensory cortex that modulates with limb-movement, as would be required for neurons that are involved in mediating proprioception. A central goal of this research is to show that afferent microstimulation can evoke natural patterns of movement-modulated activity in neurons such as this.

3) We found that high-frequency stimulation of afferent neurons provides is effective in evoking novel responses in cortical neuron, and may prove to be a viable method for transmitting additional information to the brain. That is, the ascending pathways are capable of transmitting high-frequency signals well beyond the normal range.

4) We found that varying the stimulation location in the DRG evokes differential responses in the brain. The key result of this experiment is that it demonstrates that multichannel microelectrodes provide a high degree of spatial selectivity, opening a diverse set of channels for communication with somatosensory neurons in the brain.

5) The data from the replay experiment are highly significant in providing direct evidence that multichannel microstimulation of primary afferent neurons can evoke natural patterns of neuronal activity in primary somatosensory cortex. This supports our proposal that this somatosensory neural interface can convey movement-relevant information to the brain.

List of papers submitted or published that acknowledge ARO support during this reporting period. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Weber DJ, Stein RB, Everaert DG & Prochazka A. (2007). Limb-state feedback from ensembles of simultaneously recorded dorsal root ganglion neurons. J Neural Eng 4, S168-180.

Number of Papers published in peer-reviewed journals: 1.00

(b) Papers published in non-peer-reviewed journals or in conference proceedings (N/A for none)

Number of Papers published in non peer-reviewed journals: 0.00

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts): 0

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Bourbeau DJ, Hokanson JA, and Weber DJ. A computational model for selectively stimulating peripheral sensory neurons. In: Society for Neuroscience Annual Meeting. San Diego, CA: 2007, p. 728.711.

Hokanson JA, Wagenaar JB, and Weber DJ. Neuronal responses in somatosensory cortex to multichannel microstimulation of primary afferent neurons. In: Society for Neuroscience Annual Meeting. San Diego, CA: 2007, p. 728.710.

Wagenaar JB, Sudre G, Ventura V, and Weber DJ. Quantifying somatosensory neuronal responses using conditional mutual information. In: Society for Neuroscience Annual Meeting. San Diego, CA: 2007, p. 728.712.

Weber DJ, Hokanson JA, and Wagenaar JB. Providing somatosensory feedback via multichannel microstimulation of primary afferent neurons. In: BMES Annual Fall Meeting. Los Angeles, CA: 2007.

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts): 4

(d) Manuscripts

Number of Manuscripts: 0.00

Number of Inventions:

Graduate Students

NAME	PERCENT_SUPPORTED
Joost Wagenaar	1.00
Dennis Bourbeau	0.50
FTE Equivalent:	**1.50**
Total Number:	**2**

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Faculty Supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	0.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	0.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):	0.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	0.00

Names of Personnel receiving masters degrees

NAME

Total Number:

Names of personnel receiving PHDs

NAME

Total Number:

Names of other research staff

NAME PERCENT_SUPPORTED

FTE Equivalent:

Total Number:

Sub Contractors (DD882)

Inventions (DD882)

Scientific progress and accomplishments.

We have made significant progress toward achieving our specific aims for this project. These aims are described in Appendix 1. Briefly, they include:

Specific Aim 1): Develop a technique for multichannel microstimulation of primary afferent neuronal populations in the dorsal root ganglion.

Specific Aim 2): Evaluate the effectiveness of multichannel microstimulation of primary afferent neurons in eliciting movement-related responses in primary sensory cortical (S1) neurons.

During the 12-month funding period, we completed a total of 7 acute experiments, with the goal of developing a technique for using multichannel microstimulation to activate several distinct groups of primary afferent neurons in the dorsal root ganglia (aim 1). The utility of multichannel microstimulation is for the encoding of information in the spatiotemporal patter of stimulation applied to the afferents (aim 2). To the effectiveness of afferent microstimulation, we recorded evoked neural activity in the somatosensory cortex during microstimulation with patterns that varied in 1) amplitude (stimulus current), 2) location (various channels within the DRG electrode array) and 3) rate (the frequency of microstimulation pulses applied to each DRG electrode). A summary of the most important results appears below. Key points are highlighted in bold italics font. These points are listed here without discussion, which is provided in the remaining body of this document.

Key findings:

1) Nerve-cuff recordings of afferent responses to microstimulation revealed the range of microstimulation intensities that are needed to activate the mechanoreceptive neurons, such as muscle spindles, golgi tendon organs, and cutaneous afferents that mediate haptic and proprioceptive sensations.

2) ***We have recorded neural activity in the somatosensory cortex that modulates with limb-movement, as would be required for neurons that are involved in mediating proprioception. A central goal of this research is to show that afferent microstimulation can evoke natural patterns of movement-modulated activity in neurons such as this.***

3) We found that high-frequency stimulation of afferent neurons provides is effective in evoking novel responses in cortical neuron, and may prove to be a viable method for transmitting additional information to the brain. That is, the ascending pathways are capable of transmitting high-frequency signals well beyond the normal range.

4) ***We found that varying the stimulation location in the DRG evokes differential responses in the brain. The key result of this experiment is that it demonstrates that multichannel microelectrodes provide a high degree of spatial selectivity, opening a diverse set of channels for communication with somatosensory neurons in the brain.***

5) ***The data from the replay experiment are highly significant in providing direct evidence that multichannel microstimulation of primary afferent neurons can evoke natural patterns of neuronal activity in primary somatosensory cortex. This supports our proposal that this somatosensory neural interface can convey movement-relevant information to the brain.***

Results for Aim 1:

An intense software and hardware development effort went in to achieving Aim 1, as we needed a way to dynamically program a wide variety of microstimulation patterns and simultaneously record neural activity from a large number of microelectrodes in the brain. Figure 1 shows a diagram of the animal model that was developed for testing the brain's response to multichannel microstimulation of primary afferent neurons. Arrays of microelectrodes are implanted in the dorsal root ganglia for recording and stimulating primary afferent neurons.

We created a system that uses a programmable microstimulator to apply user-defined patterns of stimulation to each electrode in the microelectrode array. Each pattern is configured according to the intensity, rate, and location of stimulation, as shown by the boxes at the bottom of figure 1. DRG stimulation evokes action potentials which propagate centrally (orthordromically) to the brain along the ascending pathways in the spinal cord. In addition, the action potentials propagate peripherally (antidromically) toward the extremities.

The antidromic action potentials are measured in a 5-pole nerve cuff wrapped around the sciatic nerve, allowing direct assessment of the number and type of neurons recruited by each pattern of stimulation. Figure 2 shows an example of the change in afferent recruitment in response to increasing intensities of microstimulation. Evoked responses measured in the 5-pole nerve cuff show the magnitude of recruitment and the type of neurons, as indicated by the conduction velocity measured during propagation through the cuff. In this example, group 1 fibers with a mean conduction velocity of 91 m/s were recruited at 4 uA intensity. At 7.5 uA, a large group of group II fibers are recruited, with a mean conduction velocity of 67 m/s. Importantly, there is no indication of small-fiber recruitment at intensities below 10 m/s. Since we want to avoid recruitment of pain fibers, which are predominantly small in caliber, this result is important in demonstrating that microstimulation in this manner avoids activation of the small-diameter pain fibers.

Data such as that demonstrated in Figure 2 provided a starting point for testing the brain's response to afferent microstimulation. These data revealed the range of microstimulation intensities that are needed to activate the mechanoreceptive neurons, such as muscle spindles, golgi tendon organs, and cutaneous afferents that mediate haptic and proprioceptive sensations.

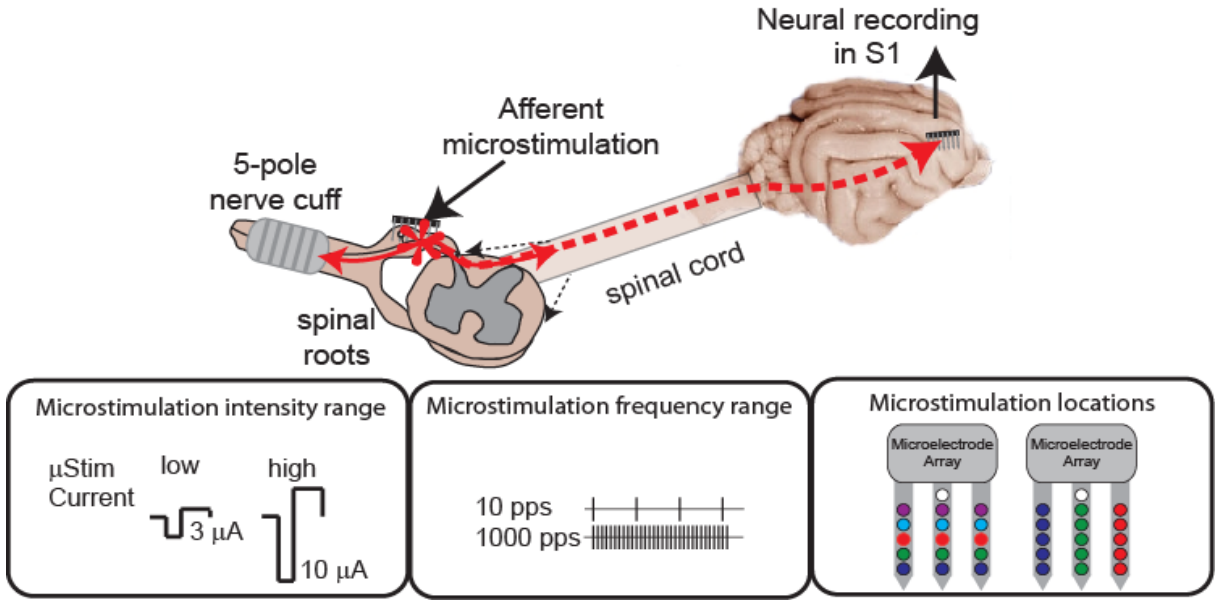


Figure 1: Animal model for testing multichannel microstimulation of primary afferent neurons.

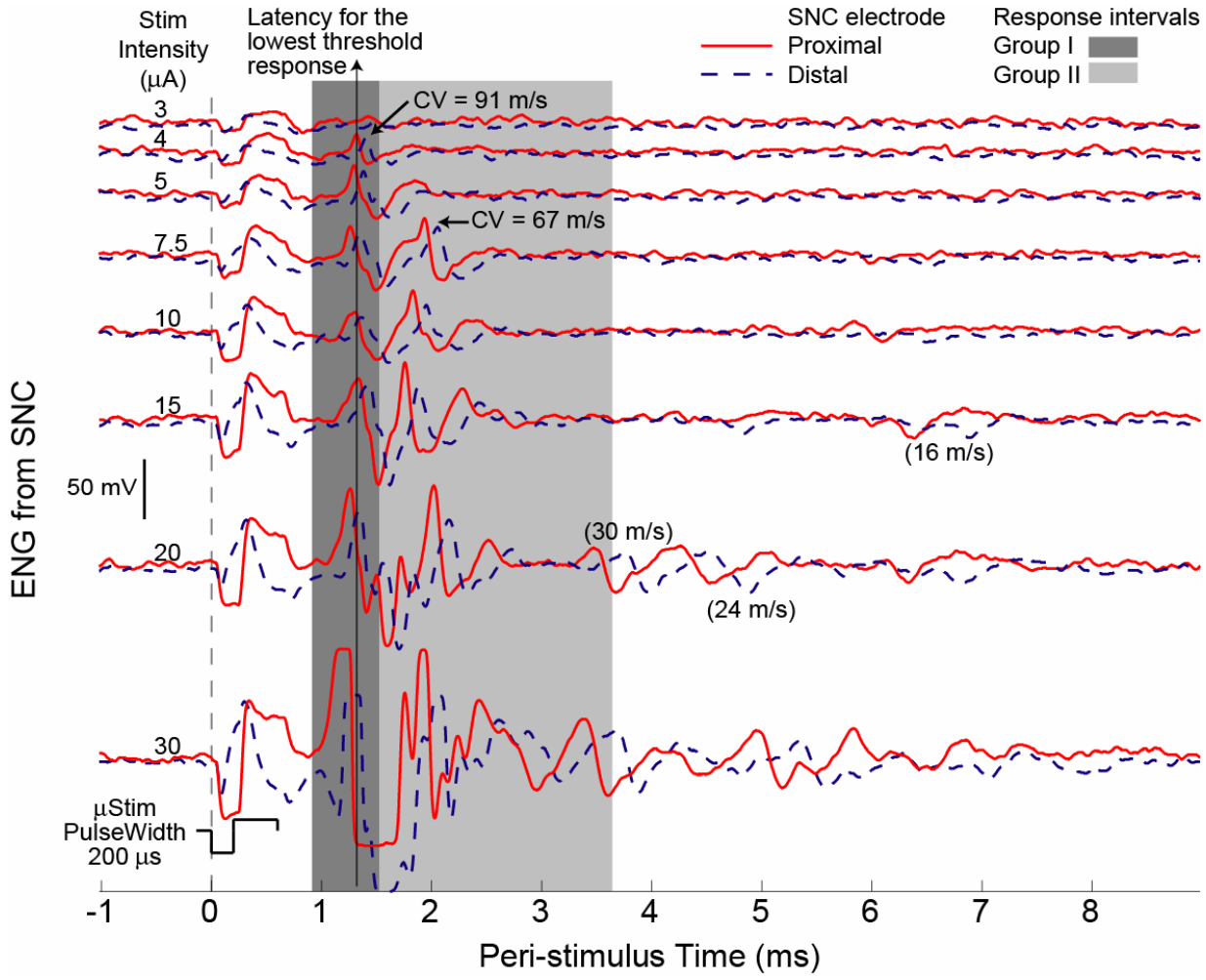


Figure 2: Progressive recruitment of primary afferent neurons during increasing levels of microstimulation in the DRG.

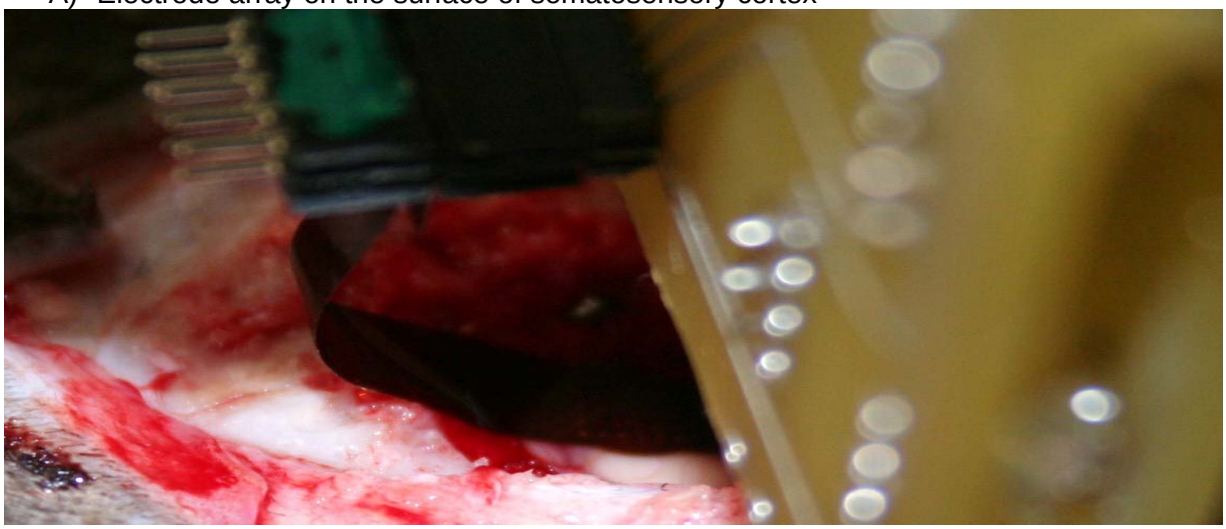
Results for Aim 2

The goal of Aim 2 is to measure the extent to which neural activity in the brain can be modulated by varying the spatiotemporal pattern of afferent microstimulation.

Receptive field mapping in somatosensory cortex

The first step in measuring the neural response in the brain is to locate the area of cortex receiving the strongest input from afferent neurons activated by the DRG microstimulation. We developed a technique that allows rapid localization by recording simultaneously the evoked potentials on a 20 electrode grid which covered a ~10 x 10 mm area of the cortical surface. Figure 3A shows a picture of the surface array placed over the exposed somatosensory cortex. Figure 3B shows an example of the responses evoked across the cortical surface during DRG microstimulation. The largest responses were evoked from channels 17 and 18, located at the rostral, medial corner of the array.

A) Electrode array on the surface of somatosensory cortex



B) Cortical surface and evoked responses measured on surface electrode array

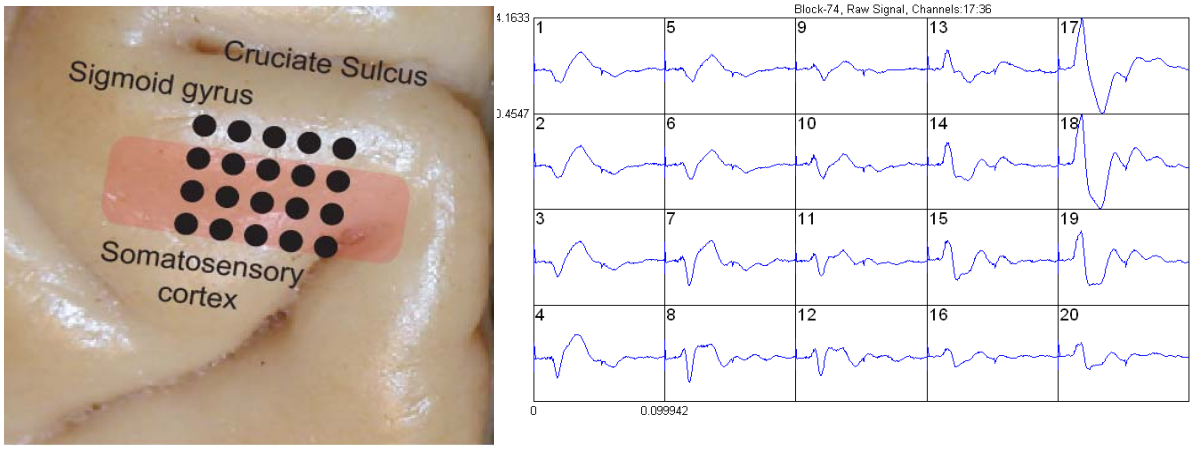


Figure 3: Receptive field mapping technique developed for identifying location of projection region for neurons activated by DRG microstimulation.

These data were used to guide the location of a penetrating microelectrode array, used to record single-unit activity and local field potentials during DRG microstimulation. Figure 4 shows a photo of a 5 x 10 array of microelectrodes implanted in the rostral, medial corner of somatosensory cortex.

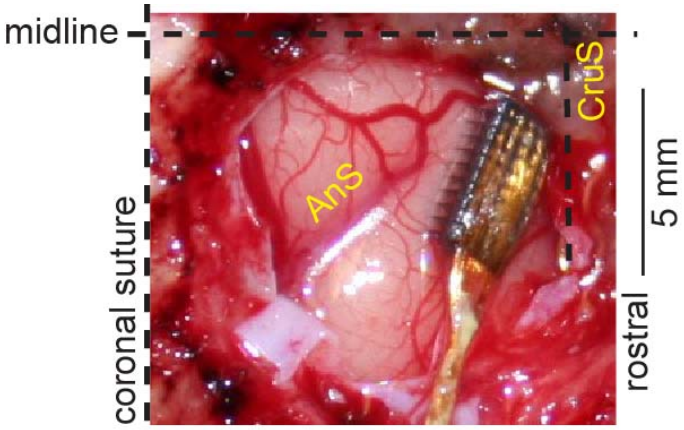


Figure 4: Microelectrode array in afferent projection zone for DRG microstimulation.

Neural recording with penetrating microelectrodes in somatosensory cortex

Single-unit activity and local-field potentials were recorded simultaneously from up to 32 microelectrodes implanted in the hindlimb afferent projection zone of somatosensory cortex (see Figure 4). Recordings were made under 2 basic conditions: 1) passive movements of the hindlimb imposed by a robotic arm, and 2) afferent microstimulation. Data from

these experiments were used to study 3 questions. First, how do neurons in somatosensory cortex respond during hindlimb-movement? Second, how do these neurons respond to varying parameters of afferent microstimulation? Third, how well does the cortical response during "replay" stimulation match the response evoked during the corresponding limb-movement? We summarize the data addressing each of these questions in turn below.

Cortical response during hindlimb-movement

Figure 5 shows response of 27 neurons in somatosensory cortex during center-out movements of the hindlimb. The lower plot in Figure 5 shows the horizontal (X) and vertical (Y) position of the toe during center-out and back movements in 8 directions. This plot shows data from 2 repetitions of this 8-direction sequence. The rasters of spike-activity in the top panel of Figure 5 show that several neurons are modulated by these movements, as indicated by variations in the density of spike-events that coincide with periods of limb-movement.

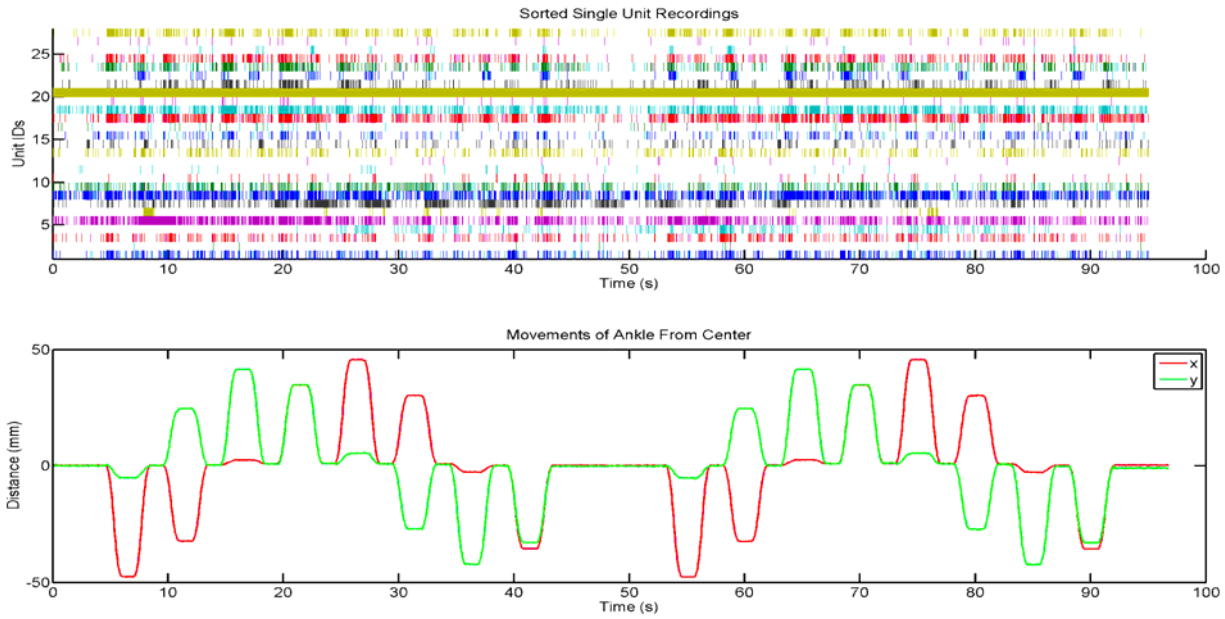


Figure 5: Spike-activity in somatosensory cortex during center-out movements of the hindlimb..

The center-out movement paradigm can be used to examine the directional-tuning properties of neurons (Georgopoulos *et al.*, 1982). Figure 6 shows an example of the directional-tuning properties of 1 neuron in somatosensory cortex. The central plot in this figure shows the isolated spike-waveforms for this neuron. The plots surrounding the perimeter display the firing rate histograms during the out-and-back sequence of movement to each location. This neuron shows a clear directional preference, responding maximally for movements upward and forward, demonstrated by high firing rates in the plots at the center and right locations in the top row.

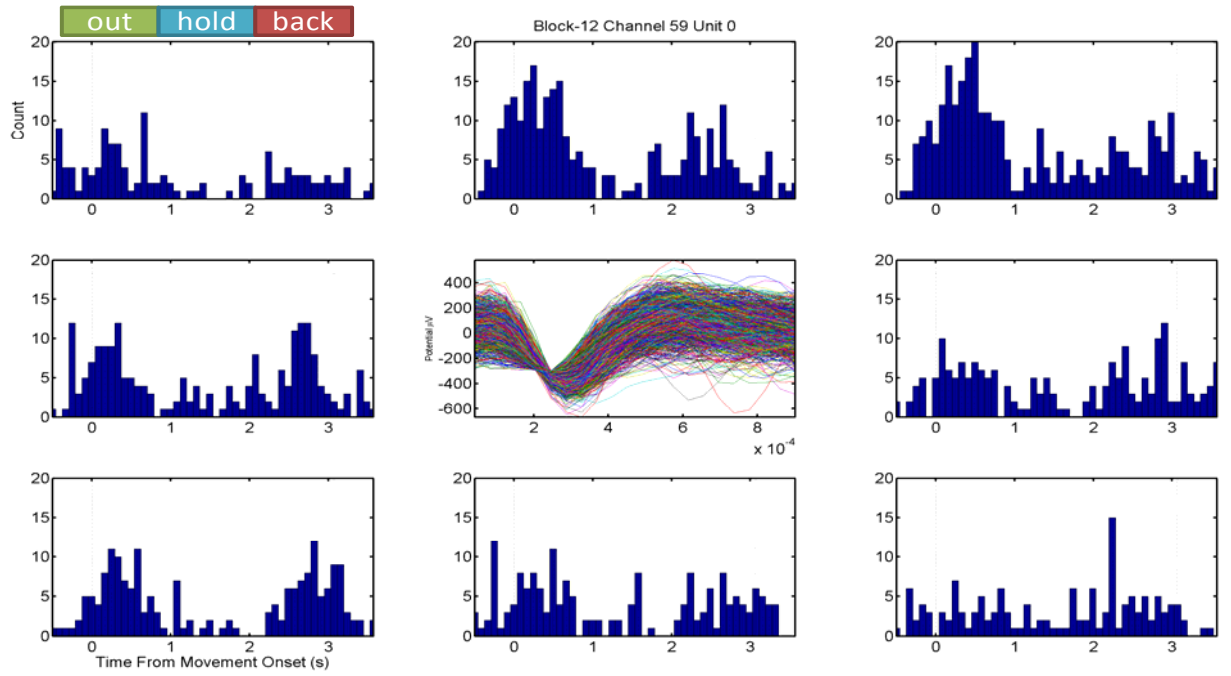


Figure 6: Rate histograms for 1 neuron during center-out-and-back movements to 8 directions.

This data is significant in that it demonstrates neural activity that modulates with limb-movement, as would be required for neurons that are involved in mediating proprioception. A central goal of this research is to show that afferent microstimulation can evoke natural patterns of movement-modulated activity in neurons such as this.

Changes in cortical response during varying parameters of microstimulation

A series of experiments were performed to examine how neural activity in somatosensory cortex changes as a function of variation in the 3 basic parameters of microstimulation: 1) intensity, 2) pulse-rate, and 3) channel location. Local field potential (LFP) recordings in the somatosensory cortex were used to measure the cortical response.

The shape and amplitude of the evoked LFP waveforms were compared across the varying levels of each parameter. Figure 7 shows the average LFP responses measured on 1 microelectrode in somatosensory cortex. As expected, the magnitude, but not the latency, of the cortical evoked response increases as the microstimulation intensity increases from 3 to 7 uA. The response appears consistently at ~15 ms latency from stimulation-onset. We attribute the increase in the magnitude of the evoked response to an increase in the number of afferent neurons recruited at higher levels of stimulation intensity.

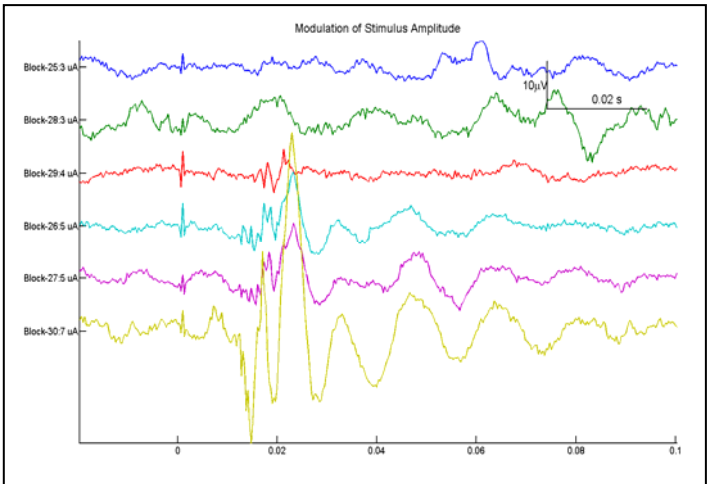


Figure 7: LFP responses from 1 channel in somatosensory cortex during increasing intensities of afferent microstimulation.

Another interesting feature of this data is that the duration of the evoked response increases at higher stimulation intensity levels. This result is likely due to increasing recruitment of smaller, slower-conducting neurons (see also Figure 2), which contribute to a later phase of cortical activation at 30 to 60 ms latency.

The stimulation pulse-rate can also influence the pattern of neural activity evoked in the brain, because temporal summation of synaptic inputs affects the strength of transmission. We explored the effects of varying rates of afferent microstimulation, to determine the extent to which high rates of stimulation can change the pattern of evoked responses in the brain.

Figure 8 shows the average LFP waveforms evoked during a 500 ms train of stimulation pulses, which varied in rate from 200 to 1000 pules/s. Data from 32 microelectrodes are shown, arranged according to their spatial location within the 5 x 10 array (implant shown in Figure 4). These data show several interesting features. First, the electrodes in the caudal (right side of figure) and medial (bottom side) portion of the array show the most consistent and largest responses. Since the array was implanted over the margin between motor and somatosensory cortex, this data shows that the response evoked in motor cortex is smaller, as expected. Second, the evoked responses show 2 distinct phases of activation, an early (primary) response appearing at ~15 ms latency, and a secondary longer-lasting response at ~45 ms latency. The second response is particularly interesting in that its magnitude varies in proportion to the microstimulation pulse-rate. Conversely, the magnitude of the primary (early) response does not change with varying pulse-rates. These differences are seen more clearly in the enlarged plot for 1 channel, shown in Figure 9. The secondary response appears similar in the 800 and 1000 Hz conditions, indicating that a saturation in the evoked activity, likely attributable to the refractory period which limits the rate at which neurons can generate action potentials. Another interesting feature of this data is that some channels exhibit only a primary or secondary

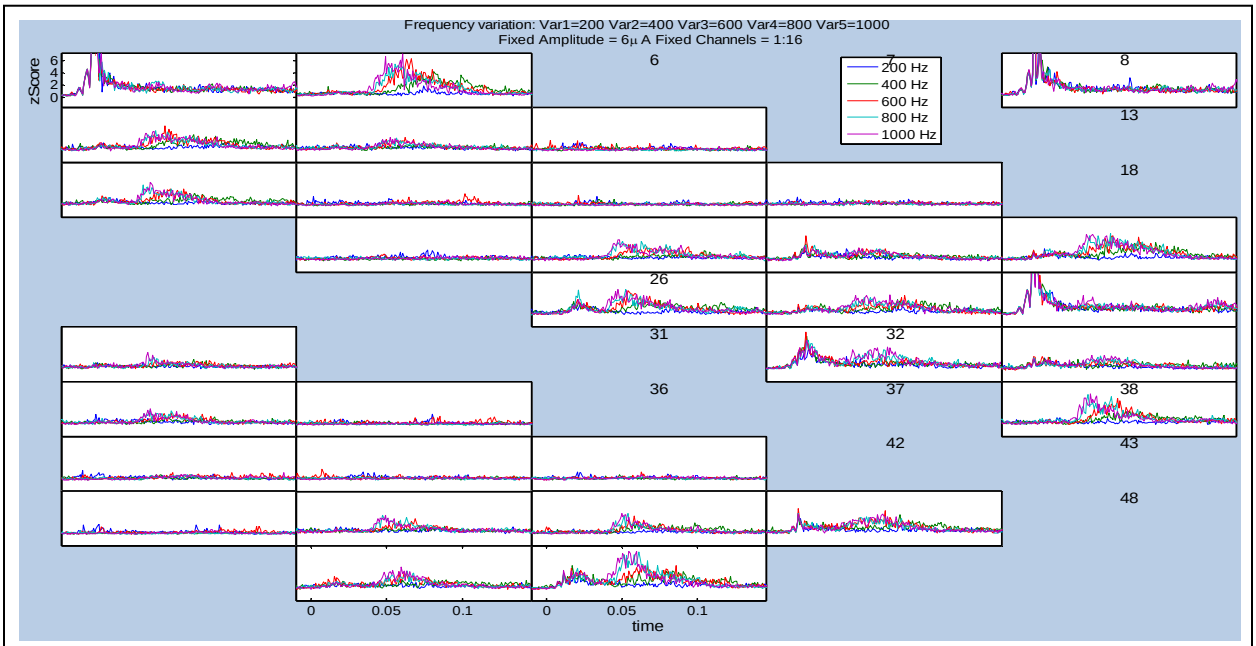


Figure 8: Average LFP response during a 500 ms train of microstimulation pulses, varied in rate from 200 to 1000 Hz. Data from 32 microelectrodes are shown.

response, for example, the 2 plots in the top left corner of Figure 8.

It is important to note that pulse-rates higher than 200 Hz are unusually fast, since the maximum firing rate of most afferent neurons rarely exceeds 200 Hz. Therefore, these data are important in demonstrating that high-frequency stimulation provides a viable

method for transmitting additional information to the brain. That is, the ascending pathways are capable of transmitting high-frequency signals well beyond the normal range.

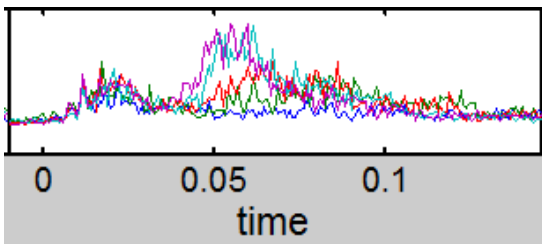


Figure 9: Enlarged view of evoked responses from 1 channel. The blue, green, red, cyan, and purple plots correspond to pulse-rates 200, 400, 600, 800, and 1000 Hz respectively.

Electrode location is another parameter that affects the pattern of neural activity evoked in the brain, since electrodes at different locations in the DRG activate different groups of neurons. We measured the variation in cortical response to stimulation applied at different locations in the DRG. Stimulation locations were defined by applying microstimulation to select groups of channels in the DRG microelectrode array. Figure 1 shows a diagram of 2 different channel-groupings that were used. The channel groupings are indicated by the colored circles, representing the location of electrodes on the 3-shank array used for these experiments. In one case, the channels were grouped according to rows, with the bottom row of electrodes positioned in the deepest part of the DRG. Similarly, the channels can also be grouped vertically, along each shank of the array.

Figure 10 shows how the pattern of evoked brain activity varies with the location of stimulation applied in the DRG. In general, the largest responses are evoked during stimulation at the middle (red) row. However, it is important to note that there is a large variation in the response patterns throughout the cortical array, highlighting the difference in connectivity between different regions of the DRG and cortex. This is not a surprising result, but it is an important step in demonstrating the utility of using multichannel microelectrodes to access a large and diverse population of afferent neurons.

The key result of this experiment is that it demonstrates that multichannel microelectrodes provide a high degree of spatial selectivity, opening a diverse set of channels for communication with somatosensory neurons in the brain.

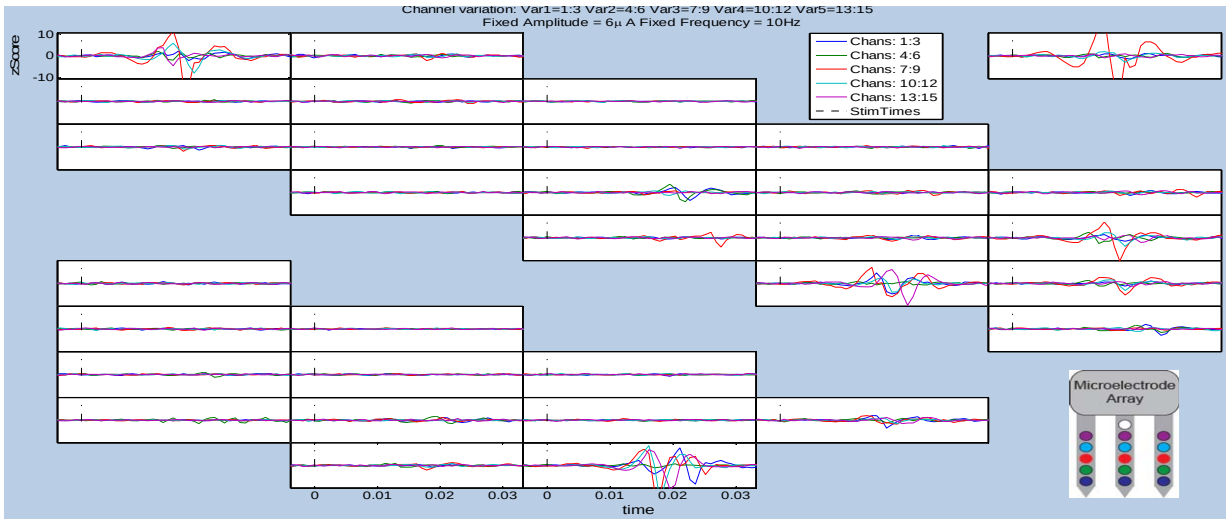


Figure 10: Average LFP response during microstimulation applied at 5 different locations in the microelectrode array. Array locations are color coded as shown in the diagram at the bottom-right.

Cortical response during replay stimulation

A final experiment was performed using the "replay" stimulation paradigm described in the proposal. During this experiment, neuronal recordings were made in the DRG and somatosensory cortex during center-out movement of the hindlimb. A 10-second portion of this data was used to test the replay condition. Spike-event times from neurons on each DRG channel were used to create a spatiotemporal pattern of afferent microstimulation. The goal was to mimic the natural pattern of afferent input present during limb-movement.

To determine the efficacy of replay stimulation, we compared the cortical neuronal activity recorded during the movement and replay conditions. A group of 34 neurons were recorded in the cortex during these trials, and 13 of these were highly correlated ($r > 0.5$) with foot-speed, indicating that they were modulated by the movement condition. The correlation between the 2 movement and replay histograms was computed for each neuron to measure the effectiveness of replay stimulation in evoking movement-like activity in the brain. Figure 11 shows exemplary results for 2 of the 13 movement-modulated neurons. Both neurons exhibit phasic patterns of activity that generally match the movement condition. However, the response during the replay

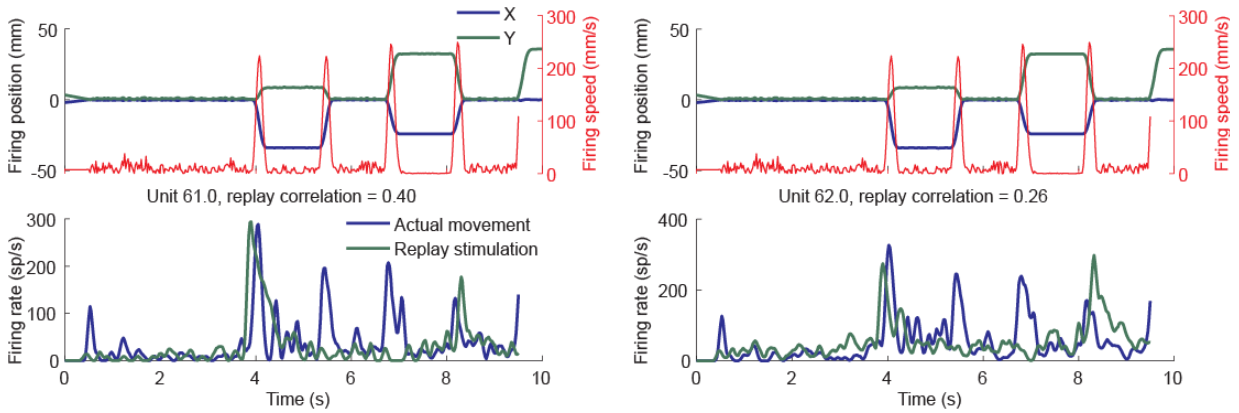


Figure 11: Foot kinematics (top plots) and neural firing rates (bottom plots) for units 61.0 (left) and 62.0 (right) during actual movement and replay stimulation that mimics the afferent input recorded during the actual movement period.

condition does not reproduce all phases of the movement-modulated response. Although the match is imperfect, the replay correlations for units 61.0 and 62.0 were 0.40 and 0.26, respectively, both correlations are highly significant ($p < 0.001$).

Lastly, we compared the replay correlations for the 13 movement-modulated neurons and the 21 remaining neurons, which had median replay correlations of 0.37 and 0.26 respectively. The scatterplot in Figure 12 shows that there is a strong linear relationship between the magnitude of the replay correlation and the magnitude of the movement-modulated correlation. This indicates that cortical neurons that are modulated by limb-movement respond better in the replay condition than those less modulated by the limb movement. The boxplot in Figure 12 shows a direct comparison of the 2 groups of unmodulated and modulated neurons. The replay correlations for the movement-modulated neurons are significantly higher ($p < 0.001$) than the replay correlations for the unmodulated neurons.

The data from the replay experiment are highly significant in providing direct evidence that multichannel microstimulation of primary afferent neurons can evoke natural patterns of neuronal activity in primary somatosensory cortex. This supports our proposal that this somatosensory neural interface can convey movement-relevant information to the brain.

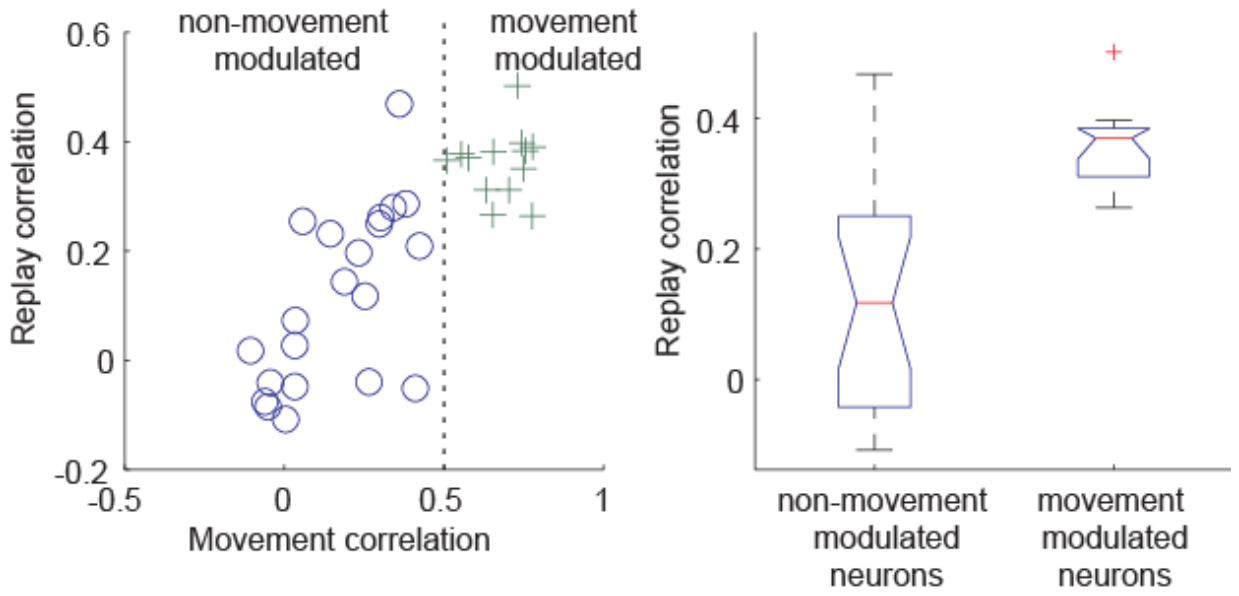


Figure 12: Dependence of replay correlation on the extent to which neurons are modulated during limb-movement. A movement correlation value of 0.5 was used to classify neurons as "movement-modulated" or unmodulated.

Reference

Georgopoulos AP, Kalaska JF, Caminiti R & Massey JT. (1982). On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J Neurosci* **2,** 1527-1537.